REMARKS/ARGUMENTS

Claims 58-62 are pending in this application.

I. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-62 remain rejected under 35 U.S.C. §101 because allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 2 of the instant Office Action).

Claims 58-62 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 3 of the instant Office Action).

Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the antibodies of Claims 58-62 possess a specific and substantial asserted utility, and that based upon this utility, one of skill in the art would know how to use the claimed antibodies without any further experimentation.

The gene amplification data disclosed in Example 114 establishes a credible, substantial and specific patentable utility for the PRO274 polypeptide and the claimed antibodies that bind it.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the PRO274 polypeptide and the claimed antibodies that bind it for the reasons previously set forth in Applicants' Responses filed on September 14, 2004 and August 31, 2005, in the Appeal Brief filed February 17, 2006, and in the Preliminary Amendment filed August 3, 2006.

Furthermore, as first discussed in Applicants' Response of September 14, 2004, Applicants rely on the gene amplification data for patentable utility of the PRO274 polypeptide and the claimed antibodies that bind it, and the gene amplification data for the gene encoding the PRO274 polypeptide is clearly disclosed in the instant specification under Example 114. As previously discussed, a ΔCt value of at least 1.0 was observed for PRO274 in at least three of the lung tumors listed in Table 9. Table 9 teaches that the nucleic acids encoding PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold amplification or 2.0 fold to 3.05-fold amplification in three types of human primary lung tumors, LT4, LT16, and LT18.

Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PRO274 polypeptide is significantly amplified in a significant number of lung tumors. Thus one of ordinary skill in the art would find it credible that PRO274 has utility as a diagnostic marker of lung tumors.

A prima facie case of lack of utility has not been established

The Examiner asserts that the disclosed gene amplification data does not provide utility for the claimed PRO274 polypeptides because allegedly "the art establishes that there is no strong connection between gene amplification and increased mRNA or protein levels." (Page 3 of the instant Office Action). In support of this assertion the Examiner refers to the previously cited articles by Pennica *et al.* and Gygi *et al.*

Applicants respectfully submit that, for the reasons previously set forth in Applicants' Responses filed on September 14, 2004 and August 31, 2005, in the Appeal Brief filed February 17, 2006, the teachings of Pennica *et al.* are specific to *WISP* genes, and say nothing about the correlation of gene amplification and protein expression in general.

Gygi *et al.*

With respect to Gygi *et al.*, Applicants reiterate that, as discussed in the Appeal Brief filed February 17, 2006, the data shown in Gygi *et al.* clearly indicates that high levels of mRNA **generally** correlate with high levels of proteins. Gygi *et al.* may teach that protein levels cannot be "predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

Applicants further respectfully submit that Futcher *et al.* (Mol. Cell. Biol. 19:7357-7368 (1999); submitted with Applicants' IDS filed August 3, 2006) also analyzed the yeast proteome

using 2D gel electrophoresis, gathering quantitative data on protein abundance for about 1,400 spots. This data was compared to mRNA abundance for each gene as determined both by SAGE (serial analysis of gene expression) and by hybridization of cRNA to oligonucleotide arrays. The authors concluded that "**several statistical methods show a strong and significant correlation between mRNA abundance and protein abundance**" (page 7360, col. 2; emphasis added).

The authors note that Gygi *et al.* completed a similar study that generated broadly similar data, but reached different conclusions. Futcher *et al.* point out that "the different conclusions are also partly due to different methods of statistical analysis, and to real differences in data." Futcher *et al.* note that Gygi *et al.* used the Pearson product-moment correlation coefficient (r_p) and point out that "a calculation of r_p is inappropriate" because the mRNA and protein abundances are not normally distributed (page 7367, col. 1). In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (r_s), an nonparametric statistic that does not require the data to be normally distributed. Using the r_s, the authors found that mRNA abundance was well correlated with protein abundance ($r_s = 0.74$). Applying this statistical approach to the data of Gygi *et al.* **also** resulted in a good correlation ($r_s = 0.59$), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were normally distributed, in order to allow calculation of an r_p. Two types of transformation (Box-Cox and logarithmic) were used, and **both** resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between

mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo***" (page 7367, col. 2; emphasis added). Thus while these lowest abundant proteins do show a poor correlation, this is almost certainly due to the less accurate methods used to measure the abundance of these proteins, and **not** to any actual lack of correlation.

References cited by Applicants

In response to the submitted textbook excerpts by Alberts and Lewin, the Examiner acknowledges that the teachings of Alberts and Lewin support that the initiation of transcription is the most common point for a cell to regulate gene expression. The Examiner asserts, however, that the initiation of transcription "is not the only means of regulating gene expression" according to the teaching of Alberts. (Page 7 of the instant Office Action).

Applicants respectfully submit that the utility standard is not **absolute certainty**. Rather, to overcome the presumption of truth that an assertion of utility by an applicant enjoys, the PTO must establish that it is **more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, Applicants **do not need** to establish that transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard. Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change in the transcription level of a gene gives rise to a change in translation level of a gene. Applicants note that both Alberts and Lewin make clear that it is far more likely than not that protein levels for any given gene are regulated at the transcriptional level. Alberts, for example, states that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added). In a similar vein, Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Thus, the utility standard is met.

With respect to Applicants' arguments regarding Meric *et al.*, the Examiner asserts that Meric teaches that "gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." (Page 8 of the instant Office Action).

Applicants respectfully submit that Meric simply summarizes the translational regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth. Meric further discusses how alterations in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecules. (see Abstract). Meric further teaches that the changes in translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggests that the translation of a cancer gene is suppressed in cancer in general, and that therefore, increased mRNA levels will not, in general, yield increased protein levels. To the contrary, Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to their normal counterparts. For instance, in patients with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation (page 974, column 1). Therefore the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the corresponding mRNA level. Thus Meric clearly supports Applicants' assertions that it is more likely than not that, in general, changes in mRNA levels are correlated with changes in protein levels.

With respect to the over one hundred additional references cited in Applicants' Preliminary Amendment filed August 3, 2006, the Examiner asserts that "[w]ith the exception of Futcher *et al.*, all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general." (Page 8 of the instant Office Action).

Applicants note that the submitted references, which represent experiments conducted by a large number of different research groups, demonstrate a trend of correlation found across proteins in general, and that this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues, under numerous biological conditions. Although only a single gene or a small group of genes was tested by each individual study group, the cumulative evidence generated by over one

hundred study groups certainly establishes that it is well-accepted in the art that a general mRNA/protein correlation exists.

The Examiner asserts that "the majority of the newly cited references by Applicants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer." (Pages 8-9 of the instant Office Action).

Applicants respectfully submit that, in fact, a number of the references submitted with Applicants' IDS filed August 3, 2006, are drawn to proteins that are not members of the above protein categories and have no obvious association with cancer. To list just a few examples, Rudlowski *et al.* examined the expression of glucose transporters 1-4; Papotti *et al.* studied three somatostatin receptors; Van der Wilt *et al.* studied deoxycytidine kinase; and Grenback *et al.* studied galanin.

Applicants further respectfully submit that, as discussed in their previous Responses and Appeal Brief, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed September 14, 2004), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being oncogenes or as having any known functions in the development and progression of cancer. Thus the art of record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Godbout *et al.*

The Examiner asserts that of the references cited by Applicants in their IDS filed July 10, 2006, only Godbout is pertinent to the issue at hand. (Page 11 of the instant Office Action). Applicants respectfully submit that, as discussed in the Preliminary Amendment filed August 3, 2006, Bea *et al.* investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in human lymphoma samples, and supports Applicants' assertion that gene amplification is correlated with both increased mRNA and protein expression.

The Examiner further asserts that Godbout *et al.* teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." (Page 11 of the instant Office Action). Applicants respectfully submit that the passage cited by the Examiner is based upon two references from 1987 and 1992. In contrast, Applicants have made of record three more recent references, published in 2002, by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Applicants' Response filed September 14, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.*

Li *et al.*

The Examiner also cites Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 13 of the instant Office Action). Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article (attached as Exhibit A), genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above the PRO274 gene showed 2.0 fold to 3.05-fold amplification in three different lung tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO274, would be expected to show a corresponding increase in transcript expression.

Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.*

In support of the assertion that "*changes* in mRNA expression frequently do not result in *changes* in protein expression" (page 16 of the instant Office Action; emphasis in original), the Examiner cites three new references, by Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.*

The Examiner cites Nagaraja *et al.* as allegedly teaching that in comparisons of expression profiles for normal breast compared to breast cancer, "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles." (Page 15 of the instant Office Action).

Applicants respectfully submit that the fact that many more transcripts than proteins were found to be differentially expressed does not mean that most mRNA changes did not result in correlating protein changes, but merely reflects the fact that expression levels were only measured at all for many fewer proteins than transcripts. In particular, the total number of proteins whose expression levels could be visualized on silver-stained gels was only about 300 (page 2332, col. 1), as compared to the approximately 14,500 genes on the microarray chips for which mRNA levels were measured (page 2336, col. 1). Since the expression levels of so many fewer proteins than transcripts were measured, it is hardly surprising that a smaller absolute number of proteins than mRNAs were found to be overexpressed, because the protein products of most of the overexpressed mRNAs would not have been among the small number of proteins identified on the gels.

The Examiner next cites Waghray *et al.*, to the effect that "for most of the proteins identified, there was no appreciable concordant change at the RNA level." (Page 15 of the instant Office Action).

Applicants emphasize that Applicants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Waghray *et al.* did not take genes which showed significant mRNA changes and check the corresponding protein levels. Instead, the authors looked at a small and unrepresentative number of proteins, and checked the corresponding mRNA levels. Waghray *et al.* acknowledge that only "[a] relatively small set of genes could be analyzed at the protein level, largely due to the limited sensitivity of 2-D PAGE" (page 1337, col. 1). In particular, while the authors examined the expression levels of16,570 genes (page 1329, col. 2), they were able to measure the expression levels of only 1031 proteins

(page 1333, col. 2). Waghray *et al.* does not teach that changes in mRNA expression were not correlated with changes in expression of the corresponding protein. All Waghray *et al.* state is that "for most of the proteins identified, there was no appreciable concordant change at the mRNA level" (page 1337, col. 2). This statement is not relevant to Applicants' assertion of utility, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. Waghray *et al.* do not contradict Applicants' assertion that changes in mRNA expression, in general, correspond to changes in expression of the corresponding protein.

Lastly, the Examiner cites Sagynaliev *et al.*, as allegedly teaching that "it is also difficult to reproduce transcriptomics results with proteomics tools." In particular, the Examiner notes that according to Sagynaliev *et al.*, of 982 genes found to be differentially expressed in human CRC, only 177 (18%) have been confirmed using proteomics technologies. (Page 16 of the instant Office Action).

The Sagynaliev *et al.* reference, titled "Web-based data warehouse on gene expression in human colorectal cancer" (emphasis added), drew conclusions based upon a literature survey of gene expression data published in human CRC, and not from experimental data. While a literature survey can be a useful tool to assist researchers, the results may greatly over-represent or under-represent certain genes, and thus the conclusions may not be generally applicable. In particular, Applicants note that, as evidenced by Nagaraja *et al.* and Waghray *et al.*, discussed above, the number of mRNAs examined in transcriptomics studies is typically much larger than the number of proteins examined in corresponding proteomics studies, due to the difficulties in detecting and resolving more than a small minority of all expressed proteins on 2D gels. Thus the fact that only 18% of all genes found to be differentially expressed in human CRC have been confirmed using proteomics technologies does not mean that the corresponding proteins are not also differentially expressed, but is most likely due to the fact that the corresponding proteins were not identified on 2D gels, and thus their expression levels remain unknown.

The authors of Sagynaliev *et al.* acknowledge the many technical problems in finding proteomic data for CRC that can be matched to transcriptomic data to see if the two correlate. The authors state that "results have been obtained using heterogeneous samples in particular cell lines, whole tissue biopsies, and epithelial cells purified from surgical speciements." However, "Results obtained in cell lines do not allow accurate comparison between normal and cancer cells, and the presence/absence of proteins of interest has to be confirmed in biopsies." (Page 3072, left column.)

In particular, the authors specifically note that "only a single study [1] provided differential display protein expression data obtained in the human patient, using whole tissue biopsy." (Page 3068, left column, second paragraph; *see also*, Table 2.) The examiner also notes and the authors state, "For CRC, there is no publication comparing mRNA and protein expression for a cohort of genes." (Page 3077, left column, last paragraph, emphasis added.)

Applicants further note that Table 2 shows that 6 out of 8 published proteomics studies were done using 2-D PAGE. However, the authors state that "2-D PAGE or 2-D DIGE have well-known technological limitations ... even under well-defined experimental conditions, 2-D PAGE parallel analysis of paired CRC samples is hampered by a significant variability." (Page 3077, left column, third paragraph.) Therefore, Applicants respectfully submit that it is well known in the art that there are problems associated with selecting only those proteins detectable by 2D gels.

Finally, the Examiner asserts that "the specification of the instant application does not teach a change in mRNA level of PRO274" because "[t]here are no teachings in the specification as to the differential expression of PRO274 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example)." (Page 16 of the instant Office Action). Applicants respectfully note that the instant specification measured gene amplification, not mRNA expression. Applicants further submit that it is well known that cancers arise from the transformation of normal tissue cells to cancerous cells, thus the observed differences in gene amplification between normal and cancerous tissues are in fact the result of previously occurring changes.

The Patent Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the previously cited Pennica *et al.* and Gygi *et al.* papers, as well as the newly cited Li, Nagaraja, Waghray, and Sagynaliev papers, do not provide sufficient reasons to doubt the statements by Applicants that PRO274 has utility. As previously discussed, the law does not require the existence of a "necessary" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately predicted." According to the authors themselves, the data in the above cited references confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and show that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard.

In fact, contrary to what the Examiner contends, the art indicates that, if a gene is overexpressed in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed September 14, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

Furthermore, in their Preliminary Amendment filed August 3, 2006, Applicants submitted a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Polakis II Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA."

The Examiner asserts that the second Polakis Declaration is insufficient to overcome the utility rejection because PRO274 does not appear in the table (Exhibit B), and allegedly it is not clear whether PRO274 shares the same characteristics as those tumor antigens tested. (Page 5 of the instant Office Action).

Applicants respectfully submit that, as discussed in their previous Responses and Appeal Brief, the standard for utility is more likely than not. Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art, that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the

encoded protein in the tumor cell relative to the normal cell." The PRO274 gene was found to be amplified in lung tumors. As discussed above and in Applicants' previous Responses, one of ordinary skill in the art would therefore expect the PRO274 mRNA to be overexpressed in the same human lung tumor samples. Accordingly, one of ordinary skill in the art would understand that the PRO274 polypeptide would be expected (more likely than not) to be overexpressed in human lung tumor samples relative to their normal human tissue counterparts, as are the majority of other molecules tested.

The Examiner further states that "levels of mRNA and protein in tumor tissue were compared to corresponding normal tissue, but the amplification levels of genomic DNA from example 114 were compared to normal human blood, not corresponding normal tissue." (Page 5 of the instant Office Action). Applicants respectfully note that the Polakis Declaration describes the results of microarray experimentation, while Example 114 of the specification discloses gene amplification data. Thus the Examiner's attempt to contrast the methodology of the two types of experiments is misplaced.

The Examiner appears to require Applicants to provide every single experimental detail involved in the testing of the mRNA/protein correlation according to the Polakis Declaration. Such a requirement is unreasonable because neither the law nor the Utility Guidelines requires Applicants to do so.

The Examiner further notes (at page 6 of the instant Office Action) that Dr. Polakis is employed by the assignee. Applicants respectfully submit that note the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position a general mRNA/protein correlation, even if Dr. Polakis is an employee of the assignee.

Based on the above arguments, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO274 polypeptide and the claimed antibodies that bind them, for example, as diagnostic markers for lung tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

Applicants therefore respectfully request withdrawal of the rejections of Claims 58-62 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned agent at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2630 P1C9**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 1, 2007

By: _____
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